REMARKS

Claims 65, 66, 68-144, and 146-157 remain pending in the application, claims 1-64, 67, and 145 having been canceled by a previous amendment. The amendments to claims 65, 94, 98 and 147 are supported in the specification at page 7, lines 6-7, and also in claims 1, 2 and 7 as originally filed. Claims 95-97 and 99-100 are amended for consistency. No new matter has been added.

Applicants thank the Examiner for withdrawing the previous rejections of the claims.

The Office action asserts at page 2 that "Applicant is essentially citing their own specification as an independent description of the state of the art" because applicants' prior response (filed November 1, 2007) pointed to a statement in McAffer et al. (US 6,863,865) as support for the nonobviousness of the claims. The McAffer et al. statement at issue was described in applicant's prior response as follows:

> McAffer describes a purportedly novel method involving a "high temperature/short time" heat treatment and asserts that it allows sterilization of a budesonide suspension "**for which this was previously believed not to be possible**." (emphasis as provided in the prior response).

The Office action notes that McAffer cited applicants' own published PCT application, WO 99/25359, as support for that statement, then dismisses applicants' argument based on McAffer et al. as "not persuasive" because of that link to applicants' own WO 99/25359. Applicants maintain that the McAffer et al. evidence is highly persuasive evidence of the state of the art as of November 24, 2000 (long after applicants' priority date), and urge the Examiner to reconsider it in the event the Office is contemplating reimposing a rejection for obviousness. McAffer et al. apparently believed that those of skill in the art before November 2000 (i.e., prior to the McAffer et al. priority date) knew of no way to sterilize a budesonide suspension successfully, and McAffer et al.'s citation of WO 99/25359 as being consistent with that belief does not detract at all from the fact that they believed it. Thus, McAffer et al. is useful for establishing what at least McAffer et al. viewed as being the state of the art at a point long after

applicants' priority date. Since the Examiner has provided no equally compelling evidence to contradict McAffer et al.'s view of the state of the art, it should be taken as established.

Rejections under 35 USC § 102(b)

Claims 65, 66, 69-117, 121-123, 127-132, 136-138, 142-144 and 146-157 are newly rejected as anticipated by Day et al. (Am. J. Rhinol., 1997), combined with two other references (Monthly Prescribing Reference (MPR) and Jonsson et al. (Drug Metab. Disp., 1995)) to support inherency. According to the Office action at page 3, Day allegedly discloses the treatment of allergic rhinitis with budesonide comprised in the commercial product marketed as Rhinocort Aqua®. MPR is cited for its description of Rhinocort Aqua® as a micronized suspension of budesonide. Jonsson is cited for its alleged teaching that the 22R epimer is more potent than the 22S epimer. The Office action acknowledges that MPR (and presumably the other cited references as well) is silent regarding the sterility of the Rhinocort Aqua® product, the particular components of the suspension that makes up this product, and whether one particular epimer of budesonide was used in this product. According to the Office action,

> [Given] that the product is a commercial pharmaceutical product, it is reasonable to expect that it is sold as a sterile product. Furthermore, given that [it] is disclosed as being used for the same method as Applicant, it is reasonable to expect that the more potent epimer is used, and it contains the instantly claimed suspension components, etc. Since the Office does not have the facilities for preparing the claimed materials and comparing them with prior art inventions, the burden is on Applicant to show a novel or unobvious difference between the claimed product and the product of the prior art.

Applicants direct the Examiner's attention to the enclosed Declaration of Ann-Kristin (Karlsson) Ekelund, one of the co-inventors of the present application. As explained in paragraph 3 of this Declaration, Rhinocort Aqua® nasal spray is manufactured and sold by AstraZeneca, the assignee of the present application and Ms. Ekelund's employer. Paragraph 4 of the Declaration explains that the budesonide in this product is a racemic mixture of both the 22R and 22S enantiomers. Paragraph 5 notes that to date the Rhinocort Aqua® product has not been sterilized prior to sale by AstraZeneca and has not been labeled as a "sterile" product.

Evidence in support of the paragraph 5 assertions is described by Ms. Ekelund in paragraphs 6-8 and 11. (Paragraph 6 in particular discusses the sterility criteria of US Pharmacopeia 23/NF18, 1995, pages 1686-1690 and 1963-1975, a term added to several of the independent claims to replace the term "sterile" with a more precise term.) Thus, the Office's assertions regarding what would be "reasonable to expect" regarding this product are simply not borne out by the facts: it was not marketed as sterile, had not been sterilized, and contained a racemic mixture of budesonide 22R/22S epimers rather than merely the 22R epimer. As all of the independent claims require that the budesonide composition either meet the criteria of sterility according to the US Pharmacopoeia 23/NF18, 1995, pages 1686-1690 and 1963-1975 (i.e., can be labeled as "sterile") or have been "sterilized," it is clear that neither the Rhinocort Aqua® nasal spray mentioned in Day et al. nor the budesonide powder used in preparation of this product satisfies all of the limitations of any of the present claims. Further, several of the dependent claims require that the budesonide be "isomerically pure" or be limited to the (22R) diastereoisomer, limitations that are plainly not met by the budesonide in the Rhinocort Aqua® nasal spray product. Accordingly, Day et al. does not anticipate any of the claims. Withdrawal of the rejection is respectfully requested.

Claims 65, 66, 68-93, 115-117, 124-126 and 146-157 are newly rejected as anticipated by Jones et al. (Respir. Med. 1994) in combination with Crompton (Lung, 1990) and Jonsson et al. to support inherency. According to the Office action at page 4, Jones allegedly teaches the administration of budesonide using the product Pulmicort Turbohaler® for the treatment of asthma, and Crompton allegedly teaches that Turbohaler devices dispense inhaled corticosteroids in the form of a micronized powder. Jonsson et al. is cited as above.

Again the Office acknowledges that the cited references are silent regarding several details, including sterility and whether the budesonide is in the form of the 22R epimer. Instead of providing evidence that the claim limitations are indeed met by this product, the Office again merely opines that it is "reasonable to expect" that they are. And once again, the facts do not bear out the Office's expectations. Applicants again direct the Examiner's attention to the

Declaration of Ann-Kristin (Karlsson) Ekelund, which notes that Pulmicort Turbohaler® dry powder inhaler is manufactured and sold by AstraZeneca (paragraph 3); that the budesonide used in this product is a racemic mixture (paragraph 4); and that the marketed product was not at any time sterilized nor sold labeled as "sterile" (paragraphs 5-8 and 11). This evidence establishes that the Pulmicort Turbohaler® mentioned in Jones et al. did not anticipate (inherently or otherwise) any of the present claims. Withdrawal of the rejection for anticipation by Jones et al. is therefore respectfully requested.

Rejections under 35 USC § 103

Claims 118-120 and 133-135 are newly rejected as obvious over Day et al. with MPR, in view of Morice et al. (Clin. Pharmacol. Ther., 1996). Morice et al. is cited for its alleged teaching of the use of nebulized budesonide for the treatment of COPD.

Applicants have established above that the Rhinocort Aqua® product described by Day et al. does not meet the criteria of any of the independent or dependent claims. Morice et al. plainly does not make up for the deficiencies of Day et al. Furthermore, as no pharmaceutically acceptable method for sterilizing budesonide was known in the art in 1997, it would not have been obvious to modify the teachings of the cited references to provide a sterile budesonide product that does meet the criteria of any of the present claims. Withdrawal of the obviousness rejection over the combination of Day et al., MPR and Morice et al. is respectfully requested.

Claims 139-141 are newly rejected as obvious over Day et al. with MPR, in view of Jones et al. Jones is cited for its alleged teaching of use of budesonide to treat asthma.

Applicants have established above that the Rhinocort Aqua® product described by Day et al. does not meet the criteria of any of the independent or dependent claims. Jones et al. plainly does not make up for the deficiencies of Day et al. Furthermore, as the art in 1997 did not know of any method for sterilizing budesonide that would have produced what would have been considered a acceptable product at that time, it would not have been obvious to modify the

teachings of the cited references to provide a sterile or sterilized budesonide product that does meet the criteria of any of the present claims. Withdrawal of the obviousness rejection over the combination of Day et al., MPR and Jones et al. is respectfully requested.

Additional budesonide products

Ms. Ekelund's Declaration provides information about two additional AstraZeneca products containing budesonide: Pulmicort Respules® suspension for inhalation and Preferid® cream (for topical use).

According to the Declaration at paragraph 9, Pulmicort Respules® has been marketed as a sterile product since 2000. Prior to the November 1997 priority date, a similar product was marketed solely in a non-sterilized form as Pulmicort® suspension for nebulizing. This non-sterilized prior art product did not meet the criteria of any of the present claims.

Preferid® cream and the budesonide incorporated into this product are discussed in the Declaration at paragraphs 14-17. According to Ms. Ekelund, AstraZeneca's records indicate that for a period from about 1980 until about 1983, the manufacturing process for the version of the Preferid® cream product that was marketed in Scandinavian countries included a step of exposing the budesonide particles to ethylene oxide gas prior to combination with the cream base to form the Preferid® cream. The specification for the product so treated stated that the product was "sterile according to Ph.Eur." Around 1983, changes in the regulatory requirements for this product in the Scandinavian countries led to abandonment of the ethylene oxide exposure step and removal of the term "sterile" from the product description for Preferid® cream. Applicants note that the ethylene oxide-treated budesonide manufactured for use in Preferid® cream and/or sold in that form did not anticipate any of the present claims, for a number of reasons.

Conclusion

Applicants submit that the claims are in condition for allowance, and such action is requested. The fees in the amount of $1,050.00 for Petition for Three Month Extension fee are being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Apply any other charges or credits to deposit account 06-1050, referencing attorney docket no. 06275-0160002.

Respectfully submitted,

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